

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/445, 31/495		A3	(11) International Publication Number: WO 00/12074 (43) International Publication Date: 9 March 2000 (09.03.00)
<p>(21) International Application Number: PCT/US99/19845</p> <p>(22) International Filing Date: 27 August 1999 (27.08.99)</p> <p>(30) Priority Data: 60/098,219 28 August 1998 (28.08.98) US 60/125,343 19 March 1999 (19.03.99) US</p> <p>(71) Applicant (for all designated States except US): SCIOS INC. [US/US]; 820 West Maude Avenue, Sunnyvale, CA 94086 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): GOEHRING, R., Richard [US/US]; 6195 Potters Lane, Pipersville, PA 18947 (US). LUEDTKE, Gregory, R. [US/US]; Apartment B, 963 La Meso Terrace, Sunnyvale, CA 94086 (US). MAVUNKEL, Babu, J. [US/US]; 1348 Avoget Terrace, Sunnyvale, CA 94087 (US). CHAKRAVARTY, Sarvajit [IN/US]; 976-2 Alpine Terrace, Sunnyvale, CA 94086 (US). DUGAR, Sundeep [IN/US]; 749 Wingate Drive, Bridgewater, NJ 08807 (US). SCHREINER, George, F. [US/US]; 12274 Leander Drive, Los Altos Hills, CA 94022 (US). LIU, David, Y. [US/US]; 201 Ferne Avenue, Palo Alto, CA 94036 (US). LEWICKI, John, A. [US/US]; 308 Escobar Avenue, Los Gatos, CA 95030 (US).</p>		<p>(74) Agents: FAVORITO, Carolyn et al.; Morrison & Foerster LLP, 2000 Pennsylvania Avenue, N.W., Washington, DC 20006-1888 (US).</p> <p>(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, EE, GE, HU, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p> <p>(88) Date of publication of the international search report: 31 August 2000 (31.08.00)</p>	
<p>(54) Title: USE OF PIPERIDINES AND/OR PIPERAZINES AS INHIBITORS OF P38-ALPHA KINASE</p> <p style="text-align: center;"> $\begin{array}{c} (Y)_n \\ \\ \text{Ar}^1 - X^1 - \text{N} \text{---} \text{C}_\text{ring} \text{---} \text{C}_\text{ring} \text{---} \text{Z} \text{---} X^2 \text{---} \text{Ar}^2 \\ \\ \text{m} \quad \text{l} \end{array} \quad (1)$ </p> <p>(57) Abstract</p> <p>The invention is directed to methods to treat conditions mediated by kinase using compounds of formula (1) and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein Z is N or CR¹, R¹ is a noninterfering substituent, each of X¹ and X² is a linker, Ar¹ and Ar² are identical or different, and represent optionally substituted C1-C20 hydrocarbyl residues wherein at least one of Ar¹ and Ar² is an optionally substituted aryl group, with the proviso that when X² is CH₂ or an isostere thereof, X¹ is CO or an isostere thereof, and Ar² is optionally substituted phenyl, Ar¹ is other than an optionally substituted indolyl, benzimidazolyl or benzotriazolyl substituent, and wherein said optionally substituted phenyl is not an optionally substituted indolyl, benzimidazolyl, or benzotriazolyl, Y is a noninterfering substituent, wherein n is an integer from 0-4, and wherein m is an integer from 0-4 and l is an integer from 0-3.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

Inten. Application No
PCT/US 99/19845

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CORP ;CHAN GEORGE W (US); BOEHM JEFFREY C (US)) 2 July 1998 (1998-07-02) cited in the application claims	1-30
X	WO 98 06715 A (RAHMAN SHIRLEY K ;SMITHKLINE BEECHAM PLC (GB); ADAMS JERRY LEROY () 19 February 1998 (1998-02-19) cited in the application claims; examples 2-4	1-30
E	WO 99 61426 A (SCIOS INC) 2 December 1999 (1999-12-02) the whole document	1-30

Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 May 2000

Date of mailing of the international search report

25/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Orviz Diaz, P

INTERNATIONAL SEARCH REPORT

II. national application No.

PCT/US 99/19845

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:

1-27

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-27

are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.:

-

because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See FURTHER INFORMATION SHEET PCT/ISA/210

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 99/19845

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to an extremely large number of possible compounds. Furthermore, the substituents are not clearly defined in the dependent claims. Claim 14, for example, mentions several cyclic moieties which cannot be considered as aryl groups. As a consequence, a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. The search had to be limited to the general inventive idea of piperidine or piperazine derivatives having P38 kinase inhibitory activity and to the compounds specifically mentioned in claim 21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/19845

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9828292	A	02-07-1998	NONE		
WO 9806715	A	19-02-1998	EP	0922042 A	16-06-1999
WO 9961426	A	02-12-1999	AU	4092099 A	13-12-1999